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THE STOCHASTIC MODELS FOR THE BEATING PROCESS OF THE CARDIAC MUSCLE CELL

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ABSTRACT. We propose the stochastic model for the beating process of cardiac muscle cells. The well-posedness and some stochastic calculus of the model problems are derived. We provide a numerical scheme for simulation and show the convergence order.

1. INTRODUCTION

The mystery of heart beat have attracted the attention of many biological researchers since lone time ago. Since it can be viewed as a process of synchronous beating of cardiac muscle cells, the biologists run various experiments to observe the beating of the cell-network, which are aim to study the role of the community effect of cardiomyocytes in the entrainment and establishment of stable beating rhythms [3, 4]. The motivation of this paper is to propose a mathematical model for the beating of cardiac muscle cells, based on the biological facts and experiment data.

Even for a single cardiac muscle cell, the mechanics of beating has not been fully understood from the biological point of view. It is known that the change of the distribution of ions is highly relevant to the beating phenomenon; however, there is no definite answer to the question of what and how the beating is triggered. By virtue of the experiment data (the distribution of beating periods), the cardiac cell beating can be considered as a process $Z(t)$ with the drift $\mu \geq 0$ and noise $\sigma\zeta(t)$ ($\sigma > 0$):

$$(1.1) \quad dZ(t) = \mu dt + \sigma dW(t),$$

where $\int_0^t \zeta(s) ds = W(t)$, and $W(t)$ is the standard Brownian motion. Here, $Z(t)$ denotes the state of cell at time t . For simplicity, we set the initial state $Z(0) = Z_0 \in [0, 1)$, and the beating state $Z(t-) := \lim_{s \uparrow t} Z(s) = 1$. Moreover, we assume the cell returns to the zero state after beating, i.e.

$$(1.2) \quad Z(t) = 0, \quad \text{for } Z(t-) = 1.$$

From the biological point of view, the cell has a short period of refractory time after beating and cannot be dragged back to the state just before the beating by noise. Hence, we assume the reflective boundary at state 0. As a result of (1.1) and (1.2), $Z(t)$ is the (μ, σ) Brownian motion in torus $[0, 1)$ with reflective boundary at 0.

To describe the mathematical model rigorously, we introduce the filtered probability space (Ω, \mathbb{F}, P) . The sample path of Ω is continuous in $[0, \infty)$ except for countably many points of discontinuity, where the left limit exists and the sample path is right-continuous. $Z(t)$ is an adapted stochastic process of (Ω, \mathbb{F}, P) . The dynamics of $Z(t)$ is determined

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by the stochastic differential equation (SDE):

$$(1.3a) \quad dZ(t) = \mu dt + \sigma dW(t) + dL(t) - dS(t),$$

$$(1.3b) \quad Z(0) = Z_0 \in [0, 1],$$

where $L(t)$ describes the reflective boundary at $Z = 0$, and $S(t)$ forces $Z(t)$ to jump back to 0 when reaching 1. To be specific, $L(t)$ satisfies (cf. [8, 11]):

$$(1.4) \quad \begin{cases} \text{(i) } L(t) \text{ is non-decreasing, continuous process, with } L(0) = 0, \\ \text{(ii) } L(t) \text{ increases only when } Z(t) = 0 \text{ (i.e. } \int_0^\infty Z(t) dL(t) = 0), \\ \text{such that } Z(t) \geq 0. \end{cases}$$

For $n = 1, 2, \dots$, and $t_0 = 0$, setting the beating time $\{t_n\}_{n \geq 1}$:

$$(1.5) \quad t_0 = 0, \quad t_n := \inf\{t > t_{n-1} : Z(t_-) = 1\}, \text{ for } n \in \mathbb{N}_+,$$

we define $S(t)$ by:

$$(1.6) \quad S(t) = n - 1 \quad \text{for } t_{n-1} \leq t < t_n.$$

From above definitions, we see that $0 \leq Z(t) < 1$, and $Z(t)$ is a right-continuous stochastic process with the jumps only at $\{t_n\}_{n \geq 1}$, where $Z(t_{n,-}) = 1$ and $Z(t_n) = 0$. Also, we have $S(t_{n,-}) = n - 1$ and $S(t_n) = n$.

In this note, we shall discuss the mathematical well-posedness of the one-cell model (1.3) and show some properties of beating period. Then, introducing some restrictions to describe the community effect of cardiomyocytes, we propose and study the two-cells model. We extend the two-cells model to the n -cells (cell-network) model, and consider the stablization of beating rhythms when increasing the cell number. The proof of several propositions and theorems are left out in this note because of page limits, for which one can refer to our forthcoming preprint [12].

2. THE ONE-CELL MODEL

There exists a unique $(Z(t), L(t), S(t))$ satisfying (1.3)–(1.6). In fact, setting $X(t) = Z_0 + \mu t + \sigma W(t)$, we have:

$$(2.1) \quad L(t) = \sup_{0 \leq s \leq t} (X(s) - S(s))_-, \quad \text{where } (\cdot)_- = -\min(\cdot, 0).$$

$X(t)$ is called the (μ, σ) -Brownian motion. We see that $L(t) \geq n$ for $t \geq t_n$, and (1.3) is equivalent to:

$$(2.2) \quad Z(t) = X(t) + L(t) - S(t).$$

The following theorem shows the unique existence of $(Z(t), L(t), S(t))$.

Theorem 2.1. *For arbitrary $x(t) \in C([0, \infty))$, with $x(0) \in [0, 1)$, we set the function $l(t)$:*

$$(2.3) \quad l(t) = \sup_{t_n \leq s \leq t} (x(s) - n)_-, \quad \text{for } t_n \leq t < t_{n+1}, \quad n = 0, 1, \dots,$$

where $t_0 = 0$, $t_n := \inf\{t > t_{n-1} : (x + l)(t_-) = n\}$ for $n \geq 1$. Then, $l(t)$ is the unique function such that:

- (1) l is continuous, non-decreasing function with $l(0) = 0$;
- (2) $z^* = x + l$ satisfies: $z^*(t) \geq n$ for $t \geq t_n$, $n = 0, 1, \dots$;
- (3) l increase only when $z^*(t) = n$, for $n = 0, 1, \dots$.

Let $x(t)$ be any path of (μ, σ) Brownian motion with initial $x(0) \in [0, 1)$, then $Z(t) + S(t) = z^*$.

Proof. Apparently, $l(t)$ given by (2.3) satisfies (i)-(iii). We only verify the uniqueness. Let $\tilde{l}(t)$ be any other solution, and set $\tilde{z} = x + \tilde{l}$, $y = \tilde{z} - z^* = \tilde{l} - l$. y is continuous, with finite total variance. Hence, we have

$$(2.4) \quad 0 \leq \frac{y(t)^2}{2} = \frac{1}{2}(\tilde{z}(t) - z^*(t))^2 = \int_0^t (\tilde{z} - z^*) d\tilde{l} + \int_0^t (z^* - \tilde{z}) dl.$$

For $s_1 = \min\{t_1, \tilde{t}_1\}$, where $\tilde{t}_n := \{t > t_{n-1} : \tilde{z}(t_-) = n\}$, $n \in \mathbb{N}_+$, we have

$$(2.5) \quad \int_0^{s_1} (\tilde{z} - z^*) d\tilde{l} = \int_{[0, s_1) \cap \{t: \tilde{z}(t)=0\}} (0 - z^*) d\tilde{l} \leq 0,$$

where we use (iii) for \tilde{l} and (ii) for z^* . Similarly, we have

$$(2.6) \quad \int_0^{s_1} (z^* - \tilde{z}) dl = \int_{[0, s_1) \cap \{t: z^*(t)=0\}} (0 - \tilde{z}) dl \leq 0.$$

In view of (2.4)-(2.6), $\tilde{z} = z^*$ for all $s \in [0, s_1)$, and $s_1 = t_1 = \tilde{t}_1$. Hence, we show the uniqueness for $n = 1$, and for arbitrary n , we can obtain the conclusion by the induction method. \square

2.1. The expectation and variance of the beating periods. For any $f \in C^2(0, 1)$ and $t \in (0, \infty)$, we have the Itô's formula for $Z(t)$ (cf. [2, §7 (4)]):

$$(2.7) \quad \begin{aligned} f(Z(t)) = & f(Z(0)) + \int_0^t \mu f'(Z(s)) + \frac{\sigma^2}{2} f''(Z(s)) ds \\ & + \int_0^t \sigma f'(Z(s)) dW(s) + \int_0^t f'(Z(t)) dL(t) \\ & - \sum_{n=1}^J (f(Z(t_n, -)) - f(Z(t_n))), \end{aligned}$$

where J is the times of cell beating, i.e. $J = \max\{n : t_n < t\}$ (t_n is defined by (1.5)).

We set the beating period $\Delta t_n = t_n - t_{n-1}$, where t_n is the beating time defined by (1.5). If $Z_0 = 0$, then $\{\Delta t_n\}_{n \geq 1}$ are independent identically distributed (i.i.d.) random variables. Using Itô's formula (2.7), it is not difficult to prove the following proposition, which shows the expectation of beating periods $\mathbb{E}(t_1)$.

Proposition 2.2. *For any $Z_0 \in [0, 1)$, we have*

$$(2.8) \quad \mathbb{E}(t_1) = \begin{cases} \frac{1}{\sigma^2}(1 - Z_0^2), & \text{for } \mu = 0, \\ \frac{1 - Z_0}{\mu} - \frac{1}{\theta\mu}(e^{-\theta Z_0} - e^{-\theta}), & \text{for } \mu > 0, \end{cases}$$

where $\theta = 2\mu/\sigma^2$.

To calculate the variance of the beating period, we consider the distribution of $Z(t)$ when $t \rightarrow \infty$. In fact, for $Z_0 = 0$, $Z(t)$ is a regenerative Markov process, and $\{t_n\}_{n \geq 1}$ are the regeneration time (i.e. the process Z after t_n becomes a probabilistic replica of $Z(t)$)

after t_{n-1} , $n \geq 1$). For any open interval $A \subset [0, 1]$, from the renewal theorem (cf. [1, (2.25) of Chapter 9]), we have

$$(2.9) \quad \lim_{t \rightarrow 0} P\{Z(t) \in A\} = \frac{1}{a} \int_0^\infty P\{Z(t) \in A, T > t\} dt.$$

We define a probability measure $\pi(\cdot)$:

$$(2.10) \quad \pi(A) = \frac{\mathbb{E}(\int_0^T 1_A(Z(t)) dt)}{E(T)}.$$

$\pi(A)$ can be viewed as the expected amount of time (normalized) such that $Z \in A$ during a regenerative cycle, or equivalently, the probability of $Z \in A$ when $t \rightarrow \infty$, i.e. (cf. [2, §4 of Chapter 5])

$$(2.11) \quad \pi(A) = \lim_{t \rightarrow \infty} P\{Z(t) \in A\}.$$

With the help of Itô's formula (2.7), we obtain the following lemma.

Lemma 2.3. *Let $p(z)$ ($z \in [0, 1]$) denote the probability density function for the distribution of $Z(t)$ when $t \rightarrow \infty$, i.e.*

$$(2.12) \quad \pi(A) = \int_A p(z) dz.$$

Then, we have:

$$(2.13) \quad p(z) = \begin{cases} 2(1-z), & \text{for } \mu = 0, \\ \frac{\theta}{e^\theta - \theta e^\theta - 1}(e^{\theta z} - e^\theta), & \text{for } \mu > 0, \end{cases}$$

where $\theta = \frac{2\mu}{\sigma^2}$.

We calculate the variance of beating period $\text{Var}(t_1)$.

Proposition 2.4. *For $Z_0 = 0$, we have*

$$(2.14) \quad \text{Var}(t_1) = \sigma^2 \mathbb{E}(t_1) \int_0^1 |f'(z)|^2 p(z) dz,$$

where f and $p(z)$ are given by Proposition (2.2) and Lemma 2.3. Via calculation, we have:

$$(2.15) \quad \text{Var}(t_1) = \begin{cases} \frac{2}{3\sigma^4}, & \text{for } \mu = 0, \\ \frac{1}{\mu\theta}(\theta + e^{-\theta} - 1), & \text{for } \mu > 0. \end{cases}$$

Remark 2.1. We have

$$(2.16) \quad \frac{\text{Var}(t_1)}{\mathbb{E}(t_1)^2} = \begin{cases} \frac{2}{3}, & \text{for } \mu = 0, \\ \frac{e^\theta(-5e^\theta + e^{-\theta} + 4 + 4\theta + 2\theta e^\theta)}{(1 + \theta e^\theta - e^\theta)^2}, & \text{for } \mu > 0. \end{cases}$$

Moreover, for $\mu > 0$, we have $\lim_{\theta \rightarrow 0} \frac{\text{Var}(t_1)}{\mathbb{E}(t_1)^2} = \frac{2}{3}$, and $\frac{\text{Var}(t_1)}{\mathbb{E}(t_1)^2}$ decreases when θ increasing.

3. THE TWO-CELLS PROBLEM

For $i = 1, 2$, let $Z_i(t) \in [0, 1]$ denote the state of cell i . To describe the beating process of two cells with communication, we introduce the potential function $V(\cdot, \cdot)$, and consider the synchronous beating due to the community effect. Here, $V(x, y)$ is the continuous function, satisfying

$$(3.1) \quad V(x, y) : [0, 1]^2 \rightarrow \mathbb{R},$$

and there exists some constant $K > 0$ such that, for any $x_i, y_i \in [0, 1]$, $i = 1, 2$,

$$(3.2) \quad |V(x_1, y_1) - V(x_2, y_2)| \leq K(|x_1 - x_2| + |y_1 - y_2|).$$

For cell i , we set the refractory period $[0, B_i)$, $B_i \in [0, 1]$, during which the cell cannot receive the influence from the outside environment. If one cell reaches the beating state and the other cell is outside its refractory period, then two cells beat synchronously and both return to zero state. Hence, for $i, j \in \{1, 2\}$ and $i \neq j$, we have two cases of cell beating.

- (1) When $Z_i(t-) = 1$, $Z_j(t-) \geq B_j$, then $Z_i(t) = Z_j(t) = 0$.
- (2) When $Z_i(t-) = 1$, $Z_j(t-) < B_j$, then $Z_i(t) = 0$ and $Z_j(t) = Z_j(t-)$.

We call case (1) the *synchronous* beating, and case (2) the *independent* beating. Let \mathbb{t}_n ($n \geq 1$) denote the time of n -th synchronous beating, i.e. $\mathbb{t}_0 = 0$, and for $n \geq 1$,

$$(3.3) \quad \mathbb{t}_n := \inf\{t > \mathbb{t}_{n-1} : Z_i(t-) = 1, Z_j(t) \in [B_j, 1), i = 1 \text{ or } 2, j \neq i\}.$$

Moreover, let $t_{n,k}^i$ ($k \geq 1, n \geq 0$) denote the time of k -th independent beating of cell i during $(\mathbb{t}_n, \mathbb{t}_{n+1})$, i.e. $t_{n,0}^i = \mathbb{t}_n$, and for $k \geq 1$,

$$(3.4) \quad t_{n,k}^i := \inf\{t > t_{n,k-1}^i : Z_i(t-) = 1, Z_j(t-) < B_j, t < \mathbb{t}_{n+1}\}.$$

For any $t > 0$, we set the number of times of synchronous beating

$$(3.5) \quad \mathbb{J} = \max\{n : \mathbb{t}_n < t\},$$

and the number of times of independent beating of cell i during $(\mathbb{t}_n, \min\{\mathbb{t}_{n+1}, t\})$:

$$(3.6) \quad J_n^i := \max\{k : t_{n,k}^i < \min\{\mathbb{t}_{n+1}, t\}\}.$$

We define the jump function

$$(3.7) \quad S_i(t) := \sum_{n=1}^{\mathbb{J}} (Z_i(\mathbb{t}_n-) - Z_i(\mathbb{t}_n)) + \sum_{n=0}^{\mathbb{J}} \sum_{k=1}^{J_n^i} (Z_i(t_{n,k}^i-) - Z_i(t_{n,k}^i)),$$

where $Z_i(\mathbb{t}_n) = Z_i(t_{n,k}^i) = 0$ and $Z_i(t_{n,k}^i-) = 1$ according to the definition of the synchronous and independent beating. Let $L_i(t)$ satisfies (1.4) with Z replaced by Z_i . We propose the stochastic model for two cells with community effect: for $i = 1, 2$,

$$(3.8a) \quad dZ_i(t) = \mu_i dt + \sigma_i dW_i(t) + dL_i(t) - dS_i(t) + V(Z_i(t), Z_j(t))dt,$$

$$(3.8b) \quad Z_i(0) = Z_{i0} \in [0, 1),$$

where $\mu_i \geq 0$, $\sigma_i > 0$ and $W_i(t)$ denotes the independent standard Brownian motion. In fact, $Z(t) := (Z_1(t), Z_2(t))$ is a regenerative Markov process, and $\{\mathbb{t}_n\}_{n \geq 1}$ is the set of the regeneration time. The well-posedness of (3.8) follows from the standard argument (cf. [8, 6]).

Theorem 3.1. *For arbitrary $V(x, y)$ satisfying (3.1) and (3.2), there exists a unique solution $(Z_i(t), L_i(t), S_i(t))_{i=1,2}$ for (3.8).*

We write the Itô's formula of $Z(t)$ for $t \in (0, \mathbb{t}_1)$, since $Z(t) = (Z_1(t), Z_2(t))$ is the probabilistic replica during every regenerative cycle $[\mathbb{t}_{n-1}, \mathbb{t}_n)$.

For any $f \in C^2((0, 1)^2)$ and $t \in (0, \mathbb{t}_1)$, we have

$$\begin{aligned}
 (3.9) \quad f(Z(t)) = & f(Z(0)) + \int_0^t \sum_{i=1}^2 \Gamma f(Z(s)) \, ds \\
 & + \int_0^t \sum_{i=1}^2 \sigma_i f_i(Z(s)) \, dW_i(s) + \int_0^t \sum_{i=1}^2 f_i(Z(s)) dL_i(s) \\
 & - \sum_{k=1}^{J_0^1} [f(1, Z_2(t_{0,k}^1)) - f(0, Z_2(t_{0,k}^1))] \\
 & - \sum_{k=1}^{J_0^2} [f(Z_1(t_{0,k}^2), 1) - f(Z_1(t_{0,k}^2), 0)],
 \end{aligned}$$

where $f_i := \frac{\partial f}{\partial z_i}$ and Γ is the elliptic operator:

$$(3.10) \quad \Gamma f := \sum_{i=1}^2 \mu_i f_i + \sum_{i=1}^2 \frac{\sigma_i^2}{2} f_{ii}, \quad \text{with } f_{ii} := \frac{\partial^2 f}{\partial z_i^2}.$$

Remark 3.1. Since L_i increases only when $Z_i = 0$, we have

$$\int_0^t f_i(Z(s)) \, dL_i(s) = \int_{(0,t) \cap \{t: Z_i(t)=0\}} f_i(Z(s)) \, dL_i(s).$$

Applying Itô's formula (3.9), we can calculate the expected value and variance of the synchronous beating period. Setting $\Delta \mathbb{t}_n = \mathbb{t}_n - \mathbb{t}_{n-1}$, we see that $\{\Delta \mathbb{t}_n\}_{n \geq 1}$ are independent identically distributed random variables for $Z(0) = (0, 0)$.

Proposition 3.2. *For initial value $Z(0) = (Z_{10}, Z_{20}) \in [0, 1]^2$, we have*

$$(3.11) \quad E(\mathbb{t}_1) = f(Z(0)),$$

where f satisfies:

$$(3.12) \quad \begin{cases} \Gamma f = -1 & \text{in } D_2 := (0, 1)^2, \\ f = 0 & \text{on } \gamma_{sb} := \{z : z_i \in (B_i, 1), \, z_j = 1, \, i \neq j\}, \\ f_i = 0 & \text{on } \gamma_{ri} := \{z : z_i = 0\}, \, i = 1, 2, \\ f(0, z_2) = f(1, z_2) & \text{for } z_2 \in (0, B_2), \\ f(z, 0) = f(z, 1) & \text{for } z_1 \in (0, B_1). \end{cases}$$

Let $p(x)$ be the distribution density of $Z(t)$ as $t \rightarrow \infty$, i.e.

$$(3.13) \quad \int_A p(x) \, dx = \lim_{t \rightarrow \infty} P\{Z(t) \in A\}, \quad \text{for any Borel set } A \subset [0, 1]^2,$$

then we have

$$(3.14) \quad \text{Var}(\mathbb{t}_1) = E(\mathbb{t}_1) \int_{[0,1]^2} \sum_{i=1}^2 \sigma_i^2 \left| \frac{\partial f}{\partial x_i} \right|^2 p(x) \, dx.$$

Proof. It follows from Itô's formula (3.9) that

$$(3.15) \quad 0 = f(Z(\mathbb{k}_1-)) = f(Z(0)) + \int_0^{\mathbb{k}_1} \Gamma f \, ds + \int_0^{\mathbb{k}_1} \sum_{i=1}^2 \sigma_i \frac{\partial f}{\partial x_i} dW_i(s) + 0 + 0.$$

Since $\Gamma f = -1$ and $\mathbb{E}(\int_0^{\mathbb{k}_1} \sum_{i=1}^2 \sigma_i \frac{\partial f}{\partial x_i} dW_i(s)) = 0$, we have

$$(3.16) \quad \mathbb{E}(\mathbb{k}_1) = f(Z(0)) + 0.$$

(3.15) yields:

$$(3.17) \quad \mathbb{k}_1^2 = f(Z(0))^2 + 2 \int_0^{\mathbb{k}_1} \sum_{i=1}^2 \sigma_i \frac{\partial f}{\partial x_i} dW_i(s) + \left(\int_0^{\mathbb{k}_1} \sum_{i=1}^2 \sigma_i \frac{\partial f}{\partial x_i} dW_i(s) \right)^2,$$

which implies

$$(3.18) \quad \mathbb{E}(\mathbb{k}_1^2) = f(Z(0))^2 + 0 + \mathbb{E} \left(\int_0^{\mathbb{k}_1} \sum_{i=1}^2 \sigma_i^2 \left| \frac{\partial f}{\partial x_i} \right|^2 ds \right).$$

By (3.13), we have

$$(3.19) \quad \begin{aligned} & \mathbb{E} \left(\int_0^{\mathbb{k}_1} \sum_{i=1}^2 \sigma_i^2 \left| \frac{\partial f}{\partial x_i} \right|^2 ds \right) \\ &= \mathbb{E} \left(\int_0^{\mathbb{k}_1} \int_{[0,1]} \sum_{i=1}^2 \sigma_i^2 \left| \frac{\partial f}{\partial x_i}(Z(s)) \right|^2 1_{dx}(Z(s)) ds \right) \\ &= \int_{[0,1]} \sum_{i=1}^2 \sigma_i^2 \left| \frac{\partial f}{\partial x_i}(x) \right|^2 \mathbb{E} \left(\int_0^{\mathbb{k}_1} 1_{dx}(Z(s)) ds \right) \\ &= \mathbb{E}(\mathbb{k}_1) \int_{[0,1]} \sum_{i=1}^2 \sigma_i^2 \left| \frac{\partial f}{\partial x_i} \right|^2 p(x) dx. \end{aligned}$$

In view of $\text{Var}(\mathbb{k}_1) = \mathbb{E}(\mathbb{k}_1^2) - \mathbb{E}(\mathbb{k}_1)^2$, we obtain (3.14). \square

Remark 3.2. The $p(x)$ of (3.13) is not easy to calculate. Let $p(t, x)$ be the distribution density of $Z(t)$, i.e.

$$(3.20) \quad \int_A p(t, x) dx = P\{Z(t) \in A\}, \quad \text{for any Borel set } A \subset [0, 1]^2.$$

Then $p(x)$ equals to the steady state of $p(t, x)$.

The following lemma on $p(t, x)$ follows from Weyl's lemma (cf. [7, §4.2, 4]) and the Itô's formula (3.9).

Lemma 3.3. $p(t, x)$ of (3.20) satisfies: for all $t \in (0, \infty)$, $i = 1, 2$, $i \neq j$,

$$(3.21) \quad \begin{cases} \frac{\partial p}{\partial t} = \Gamma_2^* p + B(p) \delta(x) & \text{in } (0, 1)^2, \\ p(x, t) = 0 & \text{on } x_i = 1, \\ F_i(p) = 0 & \text{on } x_i = 0, \, x_j \in (B_j, 1), \\ F_i(p)|_{x_i=0}^{x_i=1} = 0 & \text{for all } x_j \in (0, B_j), \\ p(x, 0) = \delta(x - Z_0), \end{cases}$$

where $\delta(x)$ is the Dirac delta function, $F_i(p) := (\mu_i + V(x_i, x_j))p - \frac{\sigma_i^2}{2} \frac{\partial p}{\partial x_i}$, $B(p) := \sum \int_{x_i=1, x_j \in (B_j, 1)} F_i(p) d\gamma$, and

$$\Gamma_{2p}^* := \sum \frac{\sigma_i^2}{2} \frac{\partial^2 p}{\partial x_i^2} - \sum \frac{\partial}{\partial x_i} [(\mu_i + V(x_i, x_j))p].$$

The exact solution f of (3.12) is not easy to obtain; therefore, in application, instead of solving (3.12), the numerical simulation of (3.8) is performed to obtain the approximation of $\mathbb{E}(\Delta t_1)$ and $\text{Var}(\Delta t_1)$. The numerical method will be introduced in Section 5.

4. THE N-CELLS PROBLEM AND THE NUMERICAL METHOD

We consider the N -cells problem. $Z_i(t)$ denotes the state of cell i at time t for $i \in \{1, \dots, N\}$. For simplicity, we consider the cell-network such that all cells are connected with each other, and every cell has zero refractory, i.e. $B_i = 0$. Hence, there exists no independent cell beating in cell-network, and we set the (synchronous) beating time $\{t_n\}_{n \geq 1}$:

$$(4.1) \quad t_0 = 0, \quad t_n = \inf\{t > t_{n-1} : Z_i(t-) = 1 \text{ for some } i \in \{1, \dots, N\}\}.$$

For arbitrary $t > 0$, let J be the number of beating times:

$$(4.2) \quad J = \max\{n : t_n < t\}.$$

We define the jump function

$$(4.3) \quad S_i(t) := \sum_{n=1}^J (Z_i(t_n-) - Z_i(t_n)),$$

where $Z_i(t_n) = 0$. Let $L_i(t)$ satisfies (1.4) with Z replaced by Z_i . The stochastic model for N -cells reads as: for $i, j \in \{1, \dots, N\}$,

$$(4.4a) \quad dZ_i(t) = \mu_i dt + \sigma_i dW_i(t) + dL_i(t) - dS_i(t) + \sum_{j \neq i} V(Z_i(t), Z_j(t)) dt,$$

$$(4.4b) \quad Z_i(0) = Z_{i0} \in [0, 1),$$

where $\mu_i \geq 0$, $\sigma_i > 0$ and $W_i(t)$ denotes the independent standard Brownian motion.

Theorem 4.1. *There exists a unique solution $(Z_i, L_i, S_i)_{i=1, \dots, N}$ for (4.4). For the simple case $\mu_i = \mu \geq 0$, $\sigma_i = \sigma > 0$ and $Z_i(0) = 0$ for all $i \in \{1, \dots, N\}$, we have $\mathbb{E}(t_1)$ decreases when N increasing.*

5. THE NUMERICAL APPROXIMATION SCHEME

We apply the Euler scheme to the 2-cells stochastic model (cf. [5, 9, 10]), which is not difficult to extend to the N -cells problem. Let $\Delta t \ll 1$ be the time-step increment, and $t_k = k\Delta t$, $k = 0, 1, \dots$. We set $\Delta W(t_k) = W(t_k) - W(t_{k-1})$. Let $\tilde{Z}_i(t_k)$ be the approximation of $Z_i(t_k)$, $i = 1, 2$. We give the Euler scheme for problem (3.8): for $i, j = 1, 2$, $i \neq j$,

$$(5.1a) \quad Y_i(t_k) = \tilde{Z}_i(t_{k-1}) + \mu_i \Delta t + V(\tilde{Z}_i(t_{k-1}), \tilde{Z}_j(t_{k-1})) + \sigma_i \Delta W_i(t_k),$$

$$(5.1b) \quad \tilde{Z}_i(t_k) = \max\{0, Y_i(t_k)\},$$

and for the case of synchronous beating, i.e. $\tilde{Z}_i(t_k) \geq 1$ and $\tilde{Z}_j(t_k) \geq B_j$, we set $\tilde{Z}_i(t_k) = \tilde{Z}_j(t_k) = 0$; for the case of independent beating, i.e. $\tilde{Z}_i(t_k) \geq 1$ and $\tilde{Z}_j(t_k) < B_j$, we set

$\tilde{Z}_i(t_k) = 0$. We consider the error in the torus domain $[0, 1)$. In the following, $|a - b|$ denotes the distance of a, b in torus $[0, 1)$, i.e. $|a - b| := \min\{\text{abs}(a - b), \text{abs}(\text{abs}(a - b) - 1)\}$, where $\text{abs}(s)$ is the absolute value of $s \in \mathbb{R}$.

Theorem 5.1. *Let $K \in \mathbb{N}$ be the maximum time step and $T_K = \delta t K$. Then we have the convergence order:*

$$(5.2) \quad E \left(\sup_k |Z_i(t_k) - \tilde{Z}_i(t_k)| \right) \leq C(T_K)(\Delta t)^{1/2-\varepsilon}, \quad \text{for any } \varepsilon \in (0, 1).$$

REFERENCES

- [1] E. Çinlar. *INtroduction to Stochastic Process*. Prentice-Hall, 1975.
- [2] J. M. Harrison. *Brownian Motion and Stochastic Flow Systems*. John Wiley & Sons, 1985.
- [3] K. Kojima, T. Kaneko, and K. Yasuda. Role of the community effect of cardiomyocyte in the in the entrainment and reestablishment of stable beating rhythms. *Biochemical and Biophysical Research Communications*, 351:209–215, 2006.
- [4] K. Kojima, T. Kaneko, and K. Yasuda. Dependence of the community effect of cultured cardiomyocytes on the cell network pattern. *Biochemical and Biophysical Research Communications*, 356:494–498, 2007.
- [5] D. Lepingle. Euler scheme for reflected stochastic differential equations. *Mathematics and Computers in Simulation*, 38:119–126, 1995.
- [6] P. L. Lions and A. S. Sznitman. Stochastic differential equations with reflecting boundary conditions. *Comm. Pure Appl. Math.*, 37:511–537, 1984.
- [7] H. P. McKean. *Stochastic Integrals*. Academic Press, 1969.
- [8] A. V. Skorokhod. Stochastic equations for diffusion processes in a bounded region. *Theory Probab. Appl.*, 6:264–274, 1961.
- [9] L. Slominski. On approximation of solutions of multidimensional sde's with reflecting boundary conditions. *Stochastic Processes and their Applications*, 50:179–219, 1994.
- [10] L. Slominski. Some remarks on approximation of solutions of sde's with reflecting boundary conditions. *Mathematics and Computers in Simulation*, 38:109–117, 1995.
- [11] H. Tanaka. Stochastic differential equations with reflecting boundary condition in convex regions. *Hiroshima Math. J.*, 9:163–177, 1979.
- [12] G. Zhou and T. Tokihiro. The stochastic models for the cardiac muscle cell beating. *preprint*, 2016.
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